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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/602,456	06/23/2003	Per Balschmidt	6460.200-US	9387

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NOVO NORDISK, INC.
PATENT DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER
LIU, SAMUEL W

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
12/12/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

nnipatent@novonordisk.com
rhaj@novonordisk.com
KSHL@novonordisk.com

Office Action Summary	Application No.	Applicant(s)	
	10/602,456	BALSCHMIDT ET AL.	
	Examiner	Art Unit	
	Samuel W. Liu	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-11 and 13-23* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11 and 13-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 1, 3-11 and 13-23 are pending.

The amendment filed 9/24/07 which amends claims 1 and 6 has been entered. The applicants' request (filed 9/24/07) for extension of time of three months has been entered. Claims 1, 3-11 and 13-23 are examined in this Office action.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

- Claims 1, 3-11 and 13-20 are again rejected under 35 U.S.C. 103(a) as being unpatentable over by Marini J. L. (US Pat. No. 6328987 B1) taken with Herschler, R. J. (US Pat. No. 4973605) and in view of Mudaliar et al. (*Diabetes Care* (1999) 22, 1501-1506).

In the patent claims 1-3, Marini teaches a composition comprising human alpha interferon 2 and methylsulfonylmethane (MSM, i.e., dimethyl sulfone), as applied to instant claim 1 and 3.

- Note that (1) the administering routes, e.g., injection (claim 6), subcutaneous (claim 7), intramuscular (claim 8), intravenous (claim 9), pulmonal (claim 10), and topical (claim 11) administrations, refer to intended use of the claimed composition and have little patentable weight; and thus, the above Martini's teaching is applicable to claims 1, 3-11, 13 and 14; and (2) the claim language, as amended, "*that act to provide tonicity or osmolarity close to that of the body fluids at the administration site*" are considered to be intended use of the claimed composition. A chemical composition and its functional properties are inseparable, i.e., if the prior art teaches the identical composition, the functional properties disclosed are necessarily present. Thus, the above reference teaching is applicable to the claims thereof.

At col. 3, lines 17-24 and columns 4-5, Marini teaches that the composition is aqueous solution or suspension, as applied to instant claims 4-5.

In patent claims 7-8, Marini teaches that topically administering the composition to a subject, as applied to instant claims 6-11.

Since claims 15-20 are directed to the human insulin analogs which are considered to be functional equivalent or analog of wild-type insulin, e.g., Asp(B28) human insulin is a fact-acting analog of human insulin as taught by Mudaliar et al., the benefit and therapeutic applicability of formulating the insulin with MSM for the administration should also be applied to the human insulin analogs thereof. Therefore, claims 15-20 are included in the rejection.

Martini does not expressly teach the concentration of MSM administered.

Herschler teaches that the suitable MSM concentration is about 5.5-10.9 mg/ml; this MSM concentration range is non-toxic (see Example 28, col. 22, line 67 to col. 23, line 5) while dosage larger than 21.9 mg/ml is lethal to the subject administered (col. 23, line 4). Considering MSM molecular weight is 90.08, "5.5-10.9 mg/ml" is equivalent to 61-121 mM, and 21.9 mg/ml to 243 mM, as applied to instant claims 1 and 3.

One of ordinary skill in the art at the time the invention was made would have prepared the pharmaceutical composition comprising MSM and bioactive agent, e.g., human alpha interferon peptide wherein the MSM concentration is in a non-toxic range ~ 60-121 mM as suggested by Herschler. One skilled in the art would have been motivated to do this because Herschler has taught that MSM has variable toxicities to the living organism (col. 22, line 60), and also Herschler has taught a lethal limit "243 mM" (see above) of MSM used, this clearly suggests that if administration dose of MSM is larger than this limit, it would cause the subject administered death. This is also because, further, Herschler has taught the suitable/useful non-toxic range "61-121 mM" of administered MSM (see above). Thus, one skilled in the art would have chosen the Herschler suggested the non-toxic MSM concentration for formulating the bioactive agent, e.g., alpha interferon, in the pharmaceutical composition according to the Marini's teaching with reasonable expectation of success.

Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

• Claims 1, 3-11 and 13-20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over by Pierce, S. W. (US Pat. No. 6924273 B2) taken with Herschler, R. J. (US Pat. No. 4973605) and in view of Mudaliar et al. (*Diabetes Care* (1999) 22, 1501-1506).

In the patent claim 10, Pierce teaches a composition comprising insulin and MSM, as applied to instant claims 1, 3 and 13-14.

- Note that (1) the administering routes, e.g., injection (claim 6), subcutaneous (claim 7), intramuscular (claim 8), intravenous (claim 9), pulmonal (claim 10), and topical (claim 11) administrations, refer to intended use of the claimed composition and have little patentable weight; and thus, the above Martini's teaching is applicable to claims 1, 3-11, 13 and 14; and (2) the claim language, as amended, "*that act to provide tonicity or osmolarity close to that of the body fluids at the administration site*" are considered to be intended use of the claimed composition. A chemical composition and its functional properties are inseparable, i.e., if the prior art teaches the identical composition, the functional properties disclosed are necessarily present. Thus, the above reference teaching is applicable to the claims thereof.

At col. 12, lines 12-14, Pierce teaches that the composition is aqueous solution or suspension, as applied to instant claims 4-5.

In the patent claim 5, Pierce teaches that the composition is suitable for administration, e.g., oral administration, as applied to instant claims 6-11. Note that the administering routes, e.g., injection (claim 6), subcutaneous (claim 7), intramuscular (claim 8), intravenous (claim 9), pulmonal (claim 10), and topical (claim 11) administrations refer to intended use of the claimed composition and have little patentable weight; and thus, the above Piece teaching is applicable to claims 6-11.

Since claims 15-20 are directed to the human insulin analogs which are considered to be functional equivalent or analog of wild-type insulin, e.g., Asp(B28) human insulin is a fact-acting analog of human insulin as taught by Mudaliar et al., the benefit and therapeutic applicability of formulating the insulin with MSM for the administration should also be applied to the human insulin analogs thereof. Therefore, claims 15-20 are included in this rejection.

Pierce does not expressly teach the concentration of MSM administered,

Herschler teaches that the suitable MSM concentration is about 5.5-10.9 mg/ml; this MSM concentration range is non-toxic (see Example 28, col. 22, line 67 to col. 23, line 5) while dosage larger than 21.9 mg/ml is lethal to the subject administered (col. 23, line 4). Considering MSM molecular weight is 90.08, "5.5-10.9 mg/ml" is equivalent to 61-121 mM, and 21.9 mg/ml to 243 mM, as applied to instant claims 1 and 3.

One of ordinary skill in the art at the time the invention was made would have prepared the pharmaceutical composition comprising MSM and bioactive agent, e.g., human alpha interferon peptide wherein the MSM concentration is in a non-toxic range ~ 60-121 mM as suggested by Herschler. One skilled in the art would have been motivated to do this because Herschler has taught that MSM has variable toxicities to the living organism (col. 22, line 60), and also Herschler has taught a lethal limit "243 mM" (see above) of MSM used, this clearly suggests that if administration dose of MSM is larger than this limit, it would cause the subject administered death. This is also because, further, Herschler has taught the suitable/useful non-toxic range "61-121 mM" of administered MSM (see above). Thus, one skilled in the art would have chosen the Herschler suggested the non-toxic MSM concentration for formulating the bioactive agent, e.g., alpha interferon, in the pharmaceutical composition according to the

Marini's teaching with reasonable expectation of success.

Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

• Claims 1, 3-11 and 13-23 are again rejected under 35 U.S.C. 103(a) as being unpatentable over by Marini J. L. (US Pat. No. 6328987 B1) in view of Herschler, R. J. (US Pat. No. 4973605) and Mudaliar et al. (*Diabetes Care* (1999) 22, 1501-1506) as applied to claims 1 and 3-20 above, and further in view of Bois D. J. D. (US Pat. No. 6576653 B2) and Drucker, D. J. (US Pat. No. 5990077).

The rejection to 1, 3-11 and 13-20 by Marini, Herschler and Mudaliar et al. has been discussed above.

Marini, Herschler and Mudaliar et al. do not expressly teach the pharmaceutical composition comprising said MSM and Gly(8)-human GLP-1 (claim 21), or Arg(34), N-ε-(γ-Glu(N-α-hexadecanoyl))-Lys- (26)-human GLP-1(7-37)OH (claim 22) or Gly(2)-human GLP-2 (claim 23).

In the patent claim 15, Bois teaches that a GLP-1 analog GLP1(7-37) is an insulinotropin and is formulated in a pharmaceutical composition for treating diabetes. Since Gly(8)-human GLP-1 and Arg(34), N-ε-(γ-Glu(N-α-hexadecanoyl))-Lys-(26)-human GLP-1(7-37)OH are considered to be functional equivalent or functional (e.g., therapeutically useful in treating diabetes) analog to insulin discussed above and useful (see "Discussion of art"), the above the references' teachings are applied to instant claims 21-22.

In the patent claim 65, Drucker teaches that the pharmaceutical composition comprising a GLP-2 is used to treat type diabetes; and in the patent claim 67, Drucker teaches the pharmaceutical composition of the GLP-2 analog, e.g., human GLP-2(1-33). Since Gly(2)-human GLP-2 is considered to be functional equivalent or functional (e.g., therapeutically useful in treating diabetes) analog to insulin discussed above, the above the references' teachings are applied to instant claim 23.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to formulates the GLP-1 or GLP-2 analog(s) with MSM for therapeutic application, e.g., treating diabetes. One skilled in the art would have been motivated to do this because the Marini's composition comprising both the therapeutic agent and MSM, and because the GLP-1 functional analogs, e.g., Gly(8)-human GLP-1 and Arg(34), N-ε-(γ-Glu(N-α-hexadecanoyl))-Lys-(26)-human GLP-1(7-37)OH is therapeutically useful (se above). This is also because Herschler has taught several benefits for formulating the therapeutic agent with MSM in the pharmaceutical composition, e.g., (i) when MSM was administered, some disorder sate, e.g., epiphysitis, in a subject was rapidly corrected with the administered MSM (col. 2, lines 30-35), (ii) pharmacologically beneficial effect in human since MSM is useful in the treatment of a surprising variety of other diseases and adverse physiological conditions (col. 2, lines 46-52), and (iii) in addition, MSM can also be used as an additive flavor or flavor enhancing property which is especially suitable for oral administration; and furthermore, MSM also can be safely administered by intravenous or parenteral injection as well as additional benefits are seen when MSM is provided in combination with the water-soluble vitamins, as taught by Herschler (col. 10, lines 27-37). Thus, one skilled in the art would have formulated any possible therapeutic

agents, e.g., GLP-1 or GLP-2 and/or analogs thereof discussed above with MSM for the therapeutic application, e.g., treating diabetes with reasonably expected success. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

• Claims 1, 3-11 and 13-23 remain rejected under 35 U.S.C. 103(a) as being unpatentable over by Pierce, S. W. (US Pat. No. 6924273 B2) in view of Herschler, R. J. (US Pat. No. 4973605) and Mudaliar et al. (*Diabetes Care* (1999) 22, 1501-1506) as applied to claims 1, 3-11 and 13-20 above, and further in view of Bois D. J. D. (US Pat. No. 6576653 B2) and Drucker, D. J. (US Pat. No. 5990077).

The rejection to 1, 3-11 and 13-20 by Pierce, Herschler and Mudaliar et al. has been discussed above.

The references Pierce, Herschler and Mudaliar et al. do not expressly teach the pharmaceutical composition comprising said MSM and Gly(8)-human GLP-1 (claim 21), or Arg(34), N-ε-(γ-Glu(N-α-hexadecanoyl))-Lys- (26)-human GLP-1(7-37)OH (claim 22) or Gly(2)-human GLP-2 (claim 23).

In the patent claim 15, Bois teaches that a GLP-1 analog GLP1(7-37) is an insulinotropin and is formulated in a pharmaceutical composition for treating diabetes. Since Gly(8)-human GLP-1 and Arg(34), N-ε-(γ-Glu(N-α-hexadecanoyl))-Lys-(26)-human GLP-1(7-37)OH are considered to be functional equivalent or functional (e.g., therapeutically useful in treating

diabetes) analog to insulin discussed above and useful (see "Discussion of art"), the above the references' teachings are applied to instant claims 21-22.

In the patent claim 65, Drucker teaches that the pharmaceutical composition comprising a GLP-2 is used to treat type diabetes; and in the patent claim 67, Drucker teaches the pharmaceutical composition of the GLP-2 analog, e.g., human GLP-2(1-33). Since Gly(2)-human GLP-2 is considered to be functional equivalent or functional (e.g., therapeutically useful in treating diabetes) analog to insulin discussed above, the above the references' teachings are applied to instant claim 23.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to formulates the GLP-1 or GLP-2 analog(s) with MSM for therapeutic application, e.g., treating diabetes. One skilled in the art would have been motivated to do this because the Marini's composition comprising both the therapeutic agent and MSM, and because the GLP-1 functional analogs, e.g., Gly(8)-human GLP-1 and Arg(34), N-ε-(γ-Glu(N-α-hexadecanoyl))-Lys-(26)-human GLP-1(7-37)OH is therapeutically useful (se above). This is also because Herschler has taught several benefits for formulating the therapeutic agent with MSM in the pharmaceutical composition, e.g., (i) when MSM was administered, some disorder sate, e.g., epiphysitis, in a subject was rapidly corrected with the administered MSM (col. 2, lines 30-35), (ii) pharmacologically beneficial effect in human since MSM is useful in the treatment of a surprising variety of other diseases and adverse physiological conditions (col. 2, lines 46-52), and (iii) in addition, MSM can also be used as an additive flavor or flavor enhancing property which is especially suitable for oral administration; and furthermore, MSM also can be safely administered by intravenous or parenteral injection as well as additional benefits are seen when

MSM is provided in combination with the water-soluble vitamins, as taught by Herschler (col. 10, lines 27-37). Thus, one skilled in the art would have formulated any possible therapeutic agents, e.g., GLP-1 or GLP-2 and/or analogs thereof discussed above with MSM for the therapeutic application, e.g., treating diabetes with reasonably expected success. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

The applicant' response to the rejections under 35 USC 103(a)

At page 5-6, the response filed 9/24/07 argues that the amended claim 1 includes functional language "that act to provide tonicity or osmolarity close to that of the body fluids at the administration site" for the disclosed pharmaceutical composition; this functional language has patentable weight. Thus, applicants request withdrawal of the 103 rejections set froth in 4/24/07 by Marini, Herschler et al. Mudaliar, Bois and Drucker, and by Pierce, Herschler et al. Mudaliar, Bois and Drucker.

The applicants' arguments are found unpersuasive because of the reasons set forth in the above rejections, and because the reasons below. The current invention is directed to the pharmaceutical composition comprising MSM and a therapeutic agent. The functional property (the "functional language" herein) is deemed to have no patentable weight, since the disclosed composition comprising the same molar range of MSM agent must have the same functional property when administered to a subject or a target site. Structural feature is inherent property of a biomolecule, functional use cannot change the structural property thereof. MSM is an "isotonic agent", (see [0084], Bayer et al. US 2003/0224973 A10); and thus, MSM has inherent capability

of provide tonicity a the site where it is administered). A chemical composition and its properties are inseparable; if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Therefore, the 103 rejections are proper and maintained.

Conclusion

No claims are allowed.

Discussion of the art

The prior art made of record and not currently relied upon in any rejections is considered pertinent to Applicants' disclosure:

• DeFelippis et al. (US Pat. No. 7022674 B2) teach that GLP-1 analogs, e.g., Gly(8)-human GLP-1 and Arg(34), N-ε-(γ-Glu(N-α-hexadecanoyl))-Lys-(26)-human GLP-1(7-37)OH (col. 1, lines 22-27 and Example 32) are useful and have improved chemical stability (abstract). This reference is not the prior art because it doe snot teach or suggest that the therapeutic agent, GLP-1 analogs is formulated with MSM.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on

the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragton, can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

Samuel W. Liu, Ph.D.
Patent Examiner, Art Unit 1656
December 3, 2007